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Long-Term Survival Data and Prognostic Factors of a Complete Response to Chemotherapy in Patients With Head and Neck Cancer Treated With Platinum-Based Induction Chemotherapy: A Hellenic Co-operative Oncology Group Study

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A group of 154 patients with locally advanced head and neck cancer, treated with platinum-based induction chemotherapy, were followed up for 5 years and several pretreatment characteristics were analyzed for possible correlation to a complete response (CR) to chemotherapy, time to progression (TTP) and overall survival (OS). Clinical stage ($p = 0.0024$) and a history of smoking ($p = 0.0125$) were selected as important prognostic factors for CR by stepwise logistic regression. We also identified response to chemotherapy ($p = 0.0120$), age ($p = 0.0066$), clinical stage ($p = 0.0363$), N stage ($p = 0.0028$), and tumor grade ($p = 0.0101$) as significant prognostic variables for TTP. Response to chemotherapy ($p < 0.0001$) and age ($p = 0.0017$) were found also significant for OS. These long-term prognostic factors which retain their prognostic significance after several years of follow-up could be helpful in the design of future trials in this patient population. Med. Pediatr. Oncol. 28:401–410, 1997.

Key words: prognostic factors; head and neck cancer; induction chemotherapy; radiation therapy

INTRODUCTION

During the last two decades induction chemotherapy has been integrated in the management of patients with locally advanced head and neck cancer (HNC), in an attempt to improve local control. Several platinum-based combinations were tested and impressive complete response (CR) rates, ranging form 30–54%, were reported [1–6]. However, a number of prospective randomized phase III trials failed to demonstrate a survival benefit in favor of chemotherapy treated patients compared to those who were managed with locoregional treatment [7–15]. Reasons for these disappointing results probably include the use of suboptimal chemotherapy and the small size of the patients population in most of the studies. The results of a recently performed overview of published randomized studies of adjuvant chemotherapy in HNC suggest that the induction chemotherapy increased absolute survival by 3.7% (95% confidence interval 0.9–6.5) [16]. The identification of prognostic factors influencing complete response (CR) to induction chemotherapy and survival of patients with HNC will facilitate the design of future phase III trials and will help to select those subgroups of patients most likely to benefit from induction chemotherapy.

We have previously evaluated and published various characteristics of 115 patients with HNC for their correlation with the achievement of a CR to chemotherapy and with improved survival [18]. Since, it has been reported for breast cancer that there is a changing importance of several prognostic factors during long-term follow-up [19], we have tested if this holds true for head and neck cancer as well. Therefore, we report our findings in 154 HNC patients with a minimum follow-up for surviving patients of 5 years. To our knowledge, analyses addressing this issue in HNC are rare in the literature.

PATIENTS AND METHODS

From August 1984 to May 1991, 154 patients with locally advanced HNC were entered in 3 consecutive phase II trials [20–22]. Eligibility criteria were the following: histologically confirmed locally advanced non-

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TABLE I. Chemotherapeutic Regimens in the 3 Consecutive HeCOG Studies

HE 1010-01 (n = 66)	HE 1010-02 (n = 49)	HE 1010-03 (n = 39)
Induction (3 cycles)	Induction (3 cycles)	Induction (3 cycles)
DDP 100 d 1	CBDCA 300 d 1	DDP 100 d 1
FU 1000 d 2–6	FU 1000 d 1–5	FU 1000 d 2–6
BLM 15 d 15,29	MTX 1200 d 14	
MIT 4 d 22	LV 250 d 15	
HYD 1000 d 23–27		
		Concurrently with RT
		CBDCA 60/week
Maintenance (2 cycles)	Maintenance (4 cycles)	Maintenance (4 cycles)
Same as induction	CBDCA 400 d 1	CBDCA 325 d 1
	BLM 15 d 1	BLM 15 d 1

DDP = cisplatin, FU = fluorouracil, in continuous infusion, BLM = bleomycin, in units, MIT = mitomycin, HYD = hydroxyurea per os, CBDCA = carboplatin, MTX = methotrexate, LV = leucovorin, all drugs except bleomycin given in mg/m^2.

metastatic (Mo) HNC, measurable or evaluable disease, normal hepatic and renal functions, platelets > 100,00/μl, leukocytes >4,000/μl, performance status (PS) >40 of Karnofsky's scale, age <75 years, absence of active ischemic heart disease, no prior therapy except a biopsy procedure, and a witnessed informed consent according to our institutional policies. All patients were initially evaluated by an ENT surgeon, a medical oncologist, and a radiotherapist. Initial examination of each patient included history, clinical examination, laryngoscopy, direct or indirect endoscopy, esophagoscopy or esophagography, complete blood count, serum electrolytes, liver and renal function tests, lactic dehydrogenase, erythrocyte sedimentation rate, electrocardiogram, audiogram, chest x-ray, bone scan, and CT-scan of the head and neck region. All patients were staged according to the AJCC/UICC guidelines [23].

Patients were treated with three cycles of induction chemotherapy followed by radiation therapy and/or surgery. Patients with laryngeal tumors were initially treated with two cycles of induction chemotherapy and those with objective response (CR or PR) received a third cycle of chemotherapy followed by radiation therapy. The chemotherapeutic regimens used in the 3 studies are shown in Table I.

Patients without a significant response at that time point underwent total laryngectomy and postoperative radiation. About 3 weeks after induction chemotherapy all patients were restaged. In most patients who demonstrated a clinical CR, multiple biopsies were taken from the primary tumor site for histologic confirmation of CR.

Prior to each cycle of chemotherapy, patients underwent a complete physical examination, complete blood count, and biochemistry. Chest x-ray and CT scan were repeated at the end of each treatment modality. Tumor measurements were performed in all patients before each cycle. CR was defined as a complete disappearance of all clinically evident disease in the primary site as well as in the involved cervical nodes for at least 4 weeks. Multiple biopsies were taken from the primary site of the tumor for histological confirmation. In all complete responders of the first 2 studies, while this was done randomly in those of the third study. Partial response (PR) was defined as a decrease of more than 50% in the sum of the products of the largest perpendicular diameters of the measurable lesions. Stable disease (SD) was defined as an objective response without satisfying the criteria of the PR or an increase of less than 25% in the absence of new lesions. Progressive disease (PD) was a more than 25% increase of the above measurements or the appearance of a new lesion. Toxicity criteria were those adopted by the WHO [24].

In cases of leucopenia of thrombocytopenia the subsequent cycle was started as soon as leukocytes were >3,800/μl and platelets > 100,000/μl. DDP was reduced by 50% if creatinine clearance was less than 50ml/min despite hydration or if the patient had a transient increase in serum creatinine over the upper normal limits. DDP was discontinued if the patient had a permanent abnormal increase in serum creatinine. CBDCA, MTX, and FU dose was reduced by 25% in all subsequent cycles if the patients had a nadir leukocyte count less than 2,000/μl or platelet count less than 50,000/μl.

The target volume to be irradiated was the primary site, and the lymph nodes of the neck and supraclavicular fossa. According to the protocol all patients should receive 70 Gy to the tumor area and prophylactically 45 Gy to the uninvolved cervical and supraclavicular lymph nodes. Five fractions per week of 1.8 Gy each were delivered. For the irradiation the patient was placed in a supine position and the primary site as well as the upper neck lymph nodes were treated with two lateral opposed fields up to 45 Gy in 4.5 weeks. After reaching this radiation dose, reduced lateral fields were used for the primary and the involved nodes, sparing the spinal cord (lateral and contralateral oblique fields were used in case of ipsilateral node involvement) up to 70 Gy in 7 weeks. Wedges were used when necessary. The uninvolved lower neck and the supraclavicular nodes were treated with an anterior field, starting 0.5 cm below the lateral fields and with a total dose of 45 Gy at 3–3.5 cm depth in 4.5 weeks with shielding of the lung apices. All fields were irradiated every day.

Two to three weeks after radiation treatment all patients were reevaluated; subsequent treatment depended on the primary site of the tumor and the status of cervical lymph nodes. Patients with carcinomas of the tongue or sinus, if operable, were surgically treated. Neck dissection was performed in patients who achieved a histologically confirmed CR in the primary site but had residual lymph nodes or relapsed only in the neck. Three to four

TABLE II. Patient Characteristics

n:	154	
Age (years)		
Median:	56	
Range:	17–75	
Sex		%
Men:	131	85
Women:	23	15
History of smoking		
No	36	23
Yes	118	77
History of alcohol abuse		
No	101	66
Yes	53	34
Performance status		
80–100:	41	27
60–80:	100	65
40–60:	13	8
Tumor site		
Nasopharynx:	47	30
Oral cavity:	17	11
Oropharynx:	22	14
Hypopharynx:	12	8
Larynx:	41	27
Paranasal sinus:	10	7
Salivary glands:	1	1
Unknown:	4	3
Clinical stage		
III	45	29
IV	109	71

TABLE III. Tumor Characteristics

		%
T stage		
T_x:	4	3
T_1:	11	7
T_2:	26	17
T_3:	63	41
T_4:	50	32
N stage		
N_0:	50	32
N_1:	28	18
N_{2a}:	18	12
N_{2b}:	32	21
N_{2c}:	14	9
N_3:	12	8
Histology		
SCC:	105	68
Undiferrentiated:	45	29
Other:	4	3
Grade		
I:	20	13
II:	52	34
III:	34	22
IV:	45	29
Unknown:	3	2

TABLE IV. Compliance to Treatment

Induction Chemotherapy	n
1 cycle:	154
2 cycle:	145
3 cycle:	136
Radiation:	135
Surgery:	19

TABLE V. Cause of IC* Discontinuation After the First Cycle

Death	6
Sudden	2
Stroke	1
Toxic	3
Progressive disease	4
Voluntary withdrawl	8
Total	24

*IC: Induction chemotherapy.

weeks after local treatment patients were treated with maintenance chemotherapy, (Table I).

Overall survival (OS) was estimated from the date of histological diagnosis to the date of the last follow-up or until the patient's death. Time to progression (TTP) was defined as the time between the date of histological diagnosis and the date of progression, documented clinically and/or radiologically. Patients who died from causes not related to the disease or the treatment were censored at that time as they were disease-free.

Statistical analysis

The present analysis of the data was performed on the ''intention to treat'' basis and thus all patients were included. The chi square test for homogeneity [24] was used to compare differences in patient characteristics or CR rates.

The prognostic variables used in the analysis for tumor response to induction chemotherapy, TTP, and OS were the following: age (<50 years vs ⩾50 years), sex (men vs women), Study (1010–01 vs 1010–02 vs 1010–03), performance status (40–60 vs > 60–80 vs 80–100), tumor location (nasopharynx vs oral cavity + oropharynx vs hypopharynx vs larynx vs others) clinical stage (III vs IV), T stage (T_x-T_2 vs T_3 vs T_4), N stage (N_0 vs N_1 vs N_2 vs N_3 or N_0 vs N_1 vs $N_2 + N_3$), grade (I + II vs III vs IV). The cut-off point of 50 was chosen for grouping age for reasons of consistency with other relevant studies.

Univariate and multivariate stepwise logistic regression [26] was used to identify prognostic factors significant for tumor response.

Also, we performed univariate analysis of TTP and OS with each of the possible prognostic factors using the Kaplan-Meier method [27] in order to estimate the survival curves. Survival curves were compared with the log-rank test [28]. Subsequently, those factors found significant in the univariate analysis were entered into a Cox proportional hazards regression model [29] in order to account for possible confounding. Response to induction chemotherapy was considered as a post-treatment-time-dependent factor and Cox analysis was performed with or without including this factor. The model was reduced

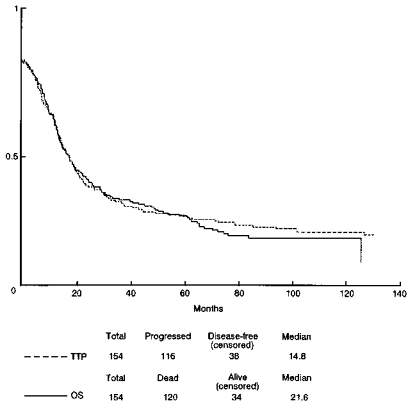

Fig. 1. Time to progression (----) and overall survival (———) of all patients.

TABLE VI. Response Rates After Induction Chemotherapy and Locoregional Treatment in the 3 Consecutive HeCOG Studies

Study	n	CR %	C.I.	n	PR %	C.I.
1010-01						
IC	17	26	15–37	31	47	35–59
IC + LTR	39	59	47–71	13	20	10–30
1010-02						
IC	10	18	8–29	26	53	42–64
IC + LTR	26	53	39–67	9	18	8–29
1010-03						
IC	14	36	21–53	17	44	28–59
IC + LTR	22	56	42–74	10	26	13–42

IC = induction chemotherapy, C.I. = 95% confidence intervals, LTR = locoregional treatment.

using a stepwise approach (with a *p*-value to enter $p = 0.05$ and a *p*-value to remove $p = 0.10$). The assumption of proportionality of Cox's model was checked using log minus log curves as well as Andersen's plots [30]. All calculations were based on two-sided alternatives. All tests were carried out using the BMDP statistical package [31].

RESULTS

Patient population

Several patient and tumor characteristics are shown in Tables II, III. There were no significant imbalances among these characteristics in the 3 studies. Patient compliance to treatment is reported in Table IV. Nine patients (6%) received only I cycle and also 9 received only 2 cycles of induction chemotherapy. Causes of treatment interruption after the first cycle are shown in Table V. A total of 135 patients (88%) were irradiated, and 19 (12%) received some form of surgery. As of March 1, 1996, 116 patients (75%) demonstrated tumor progression, while 120 (78%) died (Fig. 1). The primary site in the remaining 34 long survivors was nasopharynx (13 patients), larynx (7), oral cavity (5), paranasal sinuses (3), oropharynx (2) hypopharynx (2), salivary gland (1), and unknown (1). No patient was lost to follow-up. Seven patients (4.5%) developed a second primary neoplasm. The sites of these second primaries were lung (1 patient), base of the tongue (1), tonsil (1), nasopharynx (1), colon (1), and high grade lymphoma (2).

TABLE VII. Univariate Logistic Regression Analysis for Tumor Response (dependent variable: complete response vs all others)

Variable	n	Reference category	*p*-value (B)	Relative risk estimate
Age				
≤50	31	+		
>50	115		0.5605	N.S.
Sex				
Men	123	+		
Women	23		0.2032	N.S.
History of smoking				
No	35	11		
Yes	111		0.0092	0.3450
History of alcohol abuse				
No	97	+		
Yes	49		0.0670	N.S.
Study				
1010–01	62	+		N.S.
1010–02	48		0.4272	
1010–03	36		0.2412	
Performance status				
40–60	12	+		N.S.
60–80	93		0.7714	
80–100	41		0.8994	
Tumor location				
Nasopharynx	46	+		N.S.
Oral cavity + Oropharynx	36		0.9371	
Hypopharynx	11		0.2478	
Larynx	38		0.0656	
Others	15		0.1024	
Clinical stage				
III	43	+		
IV	103		0.0018	0.2945
T stage				
T_x-T_2	40	+		N.S.
T_3	60		0.9308	
T_4	46		0.1083	
N stage				
N_0	46	+		N.S.
N_1	27		0.7005	
N_2	62		0.2470	
N_3	11		0.3558	
Grade				
I + II	67	+		
III	33		0.1802	N.S.
IV	44		0.1246	

N.S. = not significant.

Analysis of tumor response

Response rates after induction chemotherapy and locoregional treatment in the 3 HeCOG studies are depicted in Table VI. There were no significant differences

TABLE VIII. Multiple Logistic Regression Analysis for Tumor Response (complete response vs all others)

Factor	β	df	*p*-value	Relative risk estimate
Clinical stage*	−1.22	1	0.0024	0.2950
History of smoking	−1.06	1	0.0125	0.3460

*The reference category for clinical stage is stage III and for history of smoking is no smoking.

TABLE IX. The Impact of Selected Variables on TTP Using Univariate Analysis

Variable	Median TTP (months)	n	*p*-value*
Age			
<50	50.4	33	0.0086
≥50	13.9	121	
Sex			
Men	13.9	131	N.S.
Women	21.8	23	
History of smoking			
No	30.3	36	N.S.
Yes	13.9	117	
History of alcohol abuse			
No	18.6	101	N.S.
Yes	13.8	52	
Study			
1010–01	23.1	66	0.0462
1010–02	10.5	49	
1010–03	12.3	39	
Performance status			
40–60	9.9	13	0.0948
60–80	13.2	100	
80–100	25.8	41	
Tumor Location			
Nasopharynx	26.2	47	N.S.
Oral cavity +			
Oropharynx	10.2	39	
Hypopharynx	14.0	12	
Larynx	18.6	41	
Others	10.7	15	
Clinical stage			
III	30.3	45	0.0057
IV	12.3	109	
T stage			
T_x-T_2	23.1	41	N.S.
T_3	16.5	63	
T_4	10.7	50	
N stage			
N_0	16.5	50	0.0001
N_1	21.8	28	
N_2	14.2	64	
N_3	6.2	12	
Grade			
I + II	10.5	73	0.0352
III	15.3	35	
IV	28.8	44	
Response			
CR	60.6	41	0.0010
PR + SD + PD	12.2	105	

*log rank test, N.S. = not significant.

TABLE X. The Impact of Selected Variables on TTP Using Proportional Hazards Model

(a) without response to IC as a prognostic factor

Variable	n	Reference category	Relative risk estimate	*p*-value
Age				
<50	33	+		
≥50	119		3.460	0.0074
N stage				<0.0001
N_0	49	+		
N_1	28		1.305	0.2799
N_2	63		2.037	0.2502
N_3	12		9.724	<0.0001
Grade				0.0107
I + II	73	+		
III	35		0.933	0.0252
IV	44		0.847	0.0077

Overall model $p = < 0.0001$.

(b) with response to IC as a prognostic factor

Variable	n	Reference category	Relative risk estimate	*p*-value
Response				
CR	40		0.451	0.0120
PR + SD + PD	104	+		
Age				
<50	31	+		
≥50	113		2.089	0.0066
Clinical stage				
III	42	+		
IV	102		1.845	0.0363
N stage				0.0028
N_0	45	+		
N_1	27		0.745	0.3459
N_2	61		0.794	0.3992
N_3	11		2.809	0.0093
Grade				0.0101
I + II	67	+		
III	33		0.639	0.0756
IV	44		0.492	0.0034

Overall model $p < 0.0001$. IC = induction chemotherapy
*For multiple level factors the first p-value designates the overall factor significance, while the others the individual coefficient (level) significance with respect to the reference category
CR, PR, SD, PD = see text.

among the CR rates. Both forward and backward stepwise methods, based on the factors determined significant by the univariate analysis (Table VII), selected clinical stage ($p = 0.0024$) and history of smoking ($p = 0.0125$) as significant prognostic factors (Table VIII).

Prognostic factors influencing TTP

In the univariate analysis, variables found to be strongly associated with TTP were, age ($p = 0.0086$), study ($p = 0.0462$), clinical stage ($p = 0.0057$), N stage ($p = 0.0001$), grade ($p = 0.0352$), and response to induction chemotherapy ($p = 0.001$) (Table IX). In the Cox analysis, response to induction chemotherapy ($p =$

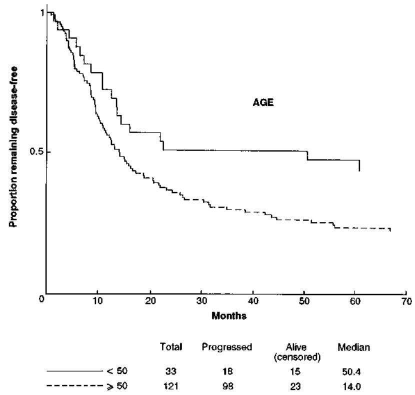

Fig. 2. Time to progression according to age (<50 vs ≥50 years). Censoring included patients who died from causes other than treatment or disease.

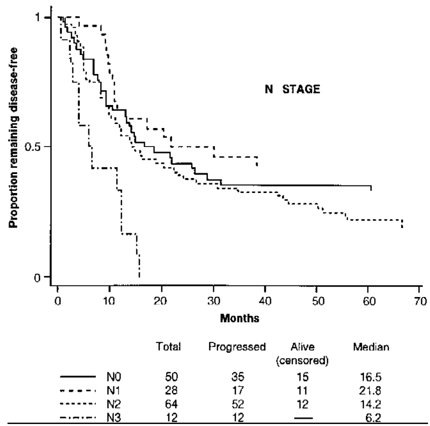

Fig. 3. Time to progression according to N stage (N0 vs N1 vs N2 vs N3). Censoring included patients who died from causes other than treatment or disease.

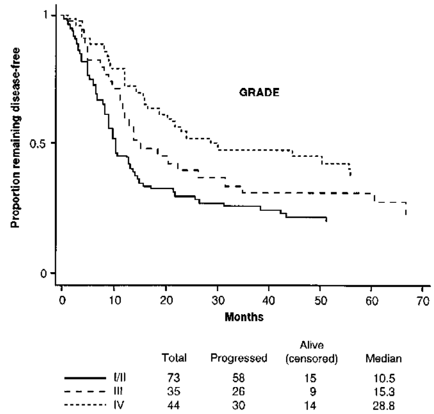

Fig. 4. Time to progression according to tumor grade (I + II vs III vs IV). Censoring included patients who died from causes other than treatment or disease.

0.0120), age ($p = 0.0066$), clinical stage ($p = 0.0363$) N stage ($p = 0.0028$), and grade ($p = 0.0101$) were retained as independently significant variables (Table X). In case the time-dependent variable response to chemotherapy was excluded from the analysis, then, age ($p = 0.0074$), N stage ($p = 0.0001$), and tumor grade ($p = 0.0252$) were identified as significant factors for TTP (Table X, Figs. 2–4).

Prognostic factors influencing OS

In the univariate analysis, significant prognostic variables were age ($p = 0.0010$), clinical stage ($p = 0.0101$), grade ($p = 0.0100$), and response to induction chemotherapy ($p < 0.0001$). Of borderline significance were performance status ($p = 0.0798$) and tumor location ($p = 0.0746$) (Table XI). The prognostic factors, finally retained in the Cox model, were, response to induction chemotherapy ($p < 0.0001$) and age ($p = 0.0017$) (Table XII). When response to chemotherapy was excluded from the analysis, then, age ($P = 0.0020$), clinical stage ($P = 0.0043$), and tumor grade ($p = 0.0170$) were selected by the model as independent prognostic variables for OS (Table XII, Figs. 5–7).

DISCUSSION

A number of meticulous retrospective analyses of the data of large series including patients with locally advanced HNC was performed during the last decade. These analyses resulted in the identification of several prognostic factors correlated with a complete response to chemotherapy or survival. Furthermore, any information regarding the categories of prognostic factors in this group of patients from several countries, allows the comparison of the natural history of locally advanced HNC in different ethnic groups.

Our patients population is a representative Greek population of patients with HNC. The majority of them was presented with a tumor located either in the nasopharynx (30%) or in the larynx (27%). This is due, firstly, to the fact that the incidence of nasopharyngeal cancer appears to be higher in Greece and other countries of the Mediterranean basin than in USA or north Europe [32,33] and secondly, to the fact that Greeks are generally heavy smokers (but not alcoholics).

Multiple regression analysis indicated that factors significantly correlated with CR to chemotherapy were stage III and a negative history of smoking. Cognetti et al [34] reported that clinical stage was predictive for overall response while T status was significant specifically for CR. T stage, N stage and performance status have been also identified by others as important prognostic factors for CR to chemotherapy [35–37].

Using Cox regression analysis we found that significant factors for TTP were response to chemotherapy, clinical stage, N stage, and tumor grade. Moreover, response to chemotherapy and age were also characterized as significant for OS.

TABLE XI. The Impact of Selected Variables on OS Using Univariate Analysis

Variable	Median Survival (months)	n	*p*-value*
Age			
<50	66.07	33	0.0010
≥50	19.27	121	
Sex			
M	20.23	131	N.S.
F	30.00	23	
History of smoking			
No	30.00	36	0.0297
Yes	19.83	118	
History of alcohol abuse			
No	23.00	101	N.S.
Yes	19.27	53	
Study			
1010–01	29.43	66	
1010–02	14.97	49	N.S.
1010–03	19.27	39	
Performance status			
40–60	13.13	13	0.0798
60–80	19.83	100	
80–100	29.83	41	
Tumor location			
Nasopharynx	49.77	47	0.0746
Oral cavity + Oropharynx	13.57	39	
Hypopharynx	14.60	12	
Larynx	25.07	41	
Others	16.93	15	
Clinical stage			
III	48.43	45	0.0101
IV	18.23	109	
T stage			
T_x-T_2	21.63	41	
T_3	27.00	63	N.S.
T_4	15.87	50	
N stage			
N_0	22.50	50	N.S.
N_1	30.00	28	
N_2	17.50	64	
N_3	19.20	12	
Grade			
I + II	15.87	73	0.0100
III	24.23	35	
IV	49.77	44	
Response			
CR	66.07	105	<0.0001
PR + SD + PD	17.50	41	

*log rank test, N.S. = Not significant
CR, PR, SD, PD = see text.

TABLE XII. The Impact of Selected Variables on OS Using Proportional Hazards Model

(a) without response to IC as a prognostic factor

Variables	n	Reference category	Relative risk estimate	*p*-value
Age				
<50	33	+		
≥50	119		2.286	0.0020
Clinical stage				
III	44	+		
IV	100		1.844	0.0043
Grade				0.0117
I + II	73	+		
III	35		0.736	0.1859
IV	44		0.506	0.0031

Overall model $p < 0.0001$.

(b) with response to IC as a prognostic factor

Variables	n	Reference category	Relative risk estimate	*p*-value
Response				
CR	41		0.374	< 0.0001
PR + SD + PD	105	+		
Age				
≤50	31	+		
≥50	115		2.349	0.0017

Overall model $p < 0.0001$. IC = induction chemotherapy
*For multiple level factors the first *p*-value designates the overall factor significance, while the others the individual coefficient (level) significance with respect to the reference category
CR, PR, SD, PD = see text.

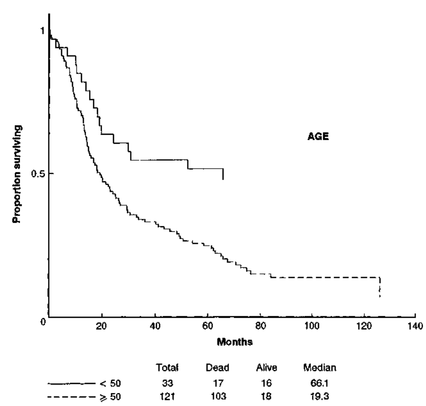

Fig. 5. Overall survival according to age (<50 vs ≥50 years).

In a subset analysis of 462 patients who were randomized in a 3-arm study (standard surgery and radiation, induction chemotherapy plus standard therapy, and induction chemotherapy plus standard therapy followed by maintenance cisplatin for 6 months) conducted by the Head and Neck Contracts Program [38], the nodal status and the site of the primary tumor had an independent and important impact on disease-free survival.

The achievement of a CR to induction chemotherapy was described as an important prognostic factor for OS in most of the published studies [34,39–41]. It has been repetitively demonstrated that patients who were fortunate to achieve a CR to chemotherapy live significantly longer than the others. Most investigators believe that induction chemotherapy acts as a selection procedure which can point out those patients (the complete responders) who will eventually have a favorite outcome independently of the type of treatment [42]. On the other hand, other investigators suggest that this may not be the case and that intrinsic tumor factors determine its responsiveness to chemotherapy [43,44].

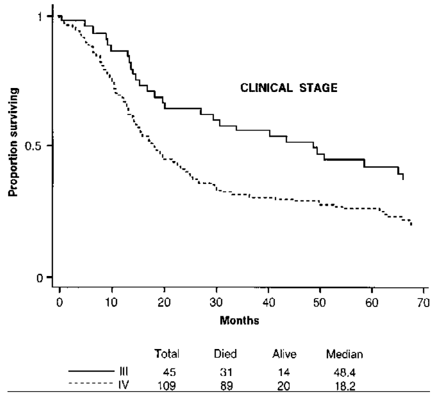

Fig. 6. Overall survival according to clinical stage (III vs IV).

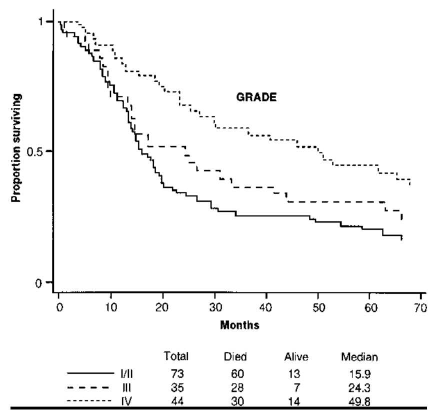

Fig. 7. Overall survival according to tumor grade (I + II vs III vs IV).

At any rate, there is an important role for induction chemotherapy in HNC, that is organ preservation. As it has been shown by the Department of Veterans Affairs Laryngeal Cancer Study Group in patients with locally advanced but operable laryngeal cancer (1), induction chemotherapy followed by radiation can preserve the larynx in 2/3 of the patients without compromising survival, and, therefore, should be offered as an alternative treatment to these patients.

Age appeared in the present study to influence OS with patients less than 50 years old having a better median survival (66 months) than older patients (19 months). This is probably correlated to the larger number of deaths from co-existent diseases such as cardiac or vascular diseases among older patients and to some extent to their poorer treatment compliance. When the time-dependent variable response to chemotherapy was excluded from the analysis, then, age, clinical stage, and tumor grade were selected by the Cox model as independent prognostic variables for OS. Clinical stage is considered by several investigators as a significant factor for survival [34,39,41]. As it was reported by Cognetti et al [34] patients with stage III disease had a double median survival compared to those with stage IV (26 months vs 13 months).

Tumor grade has been also found to influence survival differences among patients with HNC. In a RTOG study, patients without keratin in the tumor specimen had an improved survival compared to those with keratin present [45].

In conclusion, the present study identified several long-term prognostic factors significant for the achievement of a CR to induction chemotherapy, TTP, and OS of patients with locally advanced HNC. These factors, which retain their prognostic value after several years of follow-up, could be used as stratification factors in future phase III trials. Nevertheless, clinicians who treat patients with HNC cancer must be aware that induction chemotherapy failed to improve OS of these patients compared to standard locoregional treatment. The administration of concurrent chemoradiotherapy and the identification of new active drugs such as taxanes are, at present, two alternative ways to improve these results. Furthermore, emphasis should be given on the elucidation of mechanisms, at the molecular level, which lead to the development of this type of cancer.

REFERENCES

1. Rooney M, Kish J, Jacobs J, Kinzie J, Weaver A, Crissman J, Al-Sarraf M. Improved complete response rate and survival in advanced head and neck cancer after three-course induction therapy with 120-hour 5-FU infusion and cisplatin. Cancer 55: 1123–1128, 1985.
2. Weichselbaum RR, Clark JR, Miller D, Posner MR, Ervin TJ. Combined modality treatment of head and neck cancer with cisplatin, bleomycin, methotrexate-leucovorin chemotherapy. Cancer 55:2149–2155, 1985.
3. Verweij J, de Jong PC, de Mulder PHM, van der Broek P, Alexieva-Figusch J, van Putten WLJ, Schornagel JH, Ravasz LA, Snow G.B, Vermorken JB. Induction chemotherapy with cisplatin and continuous infusion 5-fluorouracil in locally far-advanced head and neck cancer. Am J Clin Oncol 12:420–424, 1989.
4. Cognetti F, Pinnaro P, Carlini P, Ruggeri EM, Impiombato FA, Del Vecchio MR, Giannarelli D, Perrino A. Neoadjuvant chemotherapy in previously untreated patients with advanced head and neck squamous cell cancer. Cancer 62:251–261, 1988.
5. Ensley J, Kish J, Tapazoglou E, Jacobs J, Weaver A, Atkinson D, Ahmed K, Mathog R, Al-Sarraf M. An intensive, five course alternating combination chemotherapy induction regimen used in patients with advanced unresectable head and neck cancer. J Clin Oncol 6:1147–1153, 1988.
6. Vokes EE, Schilsky RL, Weichselbaum RR, Kozloff MF, Panje WR. Induction chemotherapy with cisplatin, fluorouracil, and high-dose leucovorin for locally advanced head and neck cancer: A clinical and pharmacologic analysis. J Clin Oncol 8:241–247, 1990.
7. Fazekas JT, Sommer C, Kramer S. Adjuvant intravenous methotrexate or definitive radiotherapy alone for advanced squamous cancers of the oral cavity, oropharynx, supraglottic larynx of hypopharynx. Concluding report of an RTOG randomized trial on 638 patients. Int J Radiat Oncol Biol Phys 6:533–541, 1980.

8. Head and Neck Contracts Program. Adjuvant chemotherapy for advanced head and neck squamous carcinoma. Final report of the head and neck contracts program. Cancer 60:301–310, 1987.
9. Jortay A, Demard F, Dalesio O, Blanchet C, Desaulty A, Gehanno C, Lefebre JL, Molinari R, Traissac L, Dehesdin M, Kirkpatrick A. A randomized EORTC study on the effect of preoperative polychemotherapy in pyriform sinus carcinoma treated by pharyngolaryngectomy and irradiation: results from 5–10 years. Acta Chir Belg 90:115–122, 1990.
10. Laramore GE, Scott CB, Al Sarraf M, Haselow RE, Ervin TJ, Wheeler R, Jacobs JR, Schuller DE, Gahbauer RA, Schwade JG, Campbell BH. Adjuvant chemotherapy for respectable squamous cell carcinomas of the head and neck: report on intergroup study 0034. Int J Radiat Oncol Biol Phys 23:705–713, 1992.
11. Martin M, Mazeron JJ, Brun B, Vergnes L, Leievre G, Feuillade F, Juvanon JM, Haddad E, Souchal-Delacour I, Peynegre R, Pierquin B. Neoadjuvant polychemotherapy of head and neck cancer: results of a randomized study. Proc Am Soc Clin Oncol 7:152, 1988.
12. Martin M, Leievre G, Gehanno C, Depondt J, Guerrier B, Peytral C, Hazan A, Dubreuil P, Margotton A, Pellae-Cosset B. Induction carboplatin and 5-fluorouracil treatment versus no chemotherapy before locoregional treatment for oro and pharyngolaryngeal cancers: preliminary results of a randomized study. Proc Am Soc Clin Oncol 11:240, 1992.
13. Paccagnella A, Orlando A, Marchiori C, Zorat PL, Cavaniglia G, Sileni VC, Jirillo A, Tomio L, Fila G, Fede A, Endrizzi L, Bari M, Sampognaro E, Balli M, Gava A, Pappagallo GL, Fiorentino MV. Phase III trial of of initial chemotherapy in stage III or IV head and neck cancers: a study by the Gruppo di Studio sui Tumori della Testa e del Collo. J Natl Cancer Inst. 86:265–272, 1994.
14. Schuller DE, Metch B, Mattox D, Stein DW, McCraken JD. Preoperative chemotherapy in advanced resectable head and neck cancer: final report of the Southwest Oncology Group. Larysgoscope 98:1205–1211, 1988.
15. Taylor SG, Applebaum E, Showel JL, Norusis M, Holinger LD, Hutchinson JC, Murthy AK, Caldarelli DD. A randomized trial of adjuvant chemotherapy in head and neck cancer. J Clin Oncol 3:672–679, 1985.
16. Munro AJ. An overview of randomized controlled trials of adjuvant chemotherapy in head and neck cancer. Brit J Cancer 71:83–91, 1995.
17. The Department of Veterans Affairs Laryngeal Cancer Study Group. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. N Engl J Med 324:1685–1690, 1991.
18. Fountzilas G, Kosmidis P, Beer M, Sridhar KS, Banis K, Vritsios A, Daniilidis J. Factors influencing complete response and survival in patients with head and neck cancer treated with platinum-based chemotherapy. Ann Oncol 3:553–558, 1992.
19. Lipponen P, Aaltomaa S, Eskelinen M, Kosma V-M, Marin S, Syrjanen K. The changing importance of prognostic factors in breast cancer during long-term follow-up. Int J Cancer 51:698–702, 1992.
20. Fountzilas G, Daniilidis J, Sridhar SK, Kalogera-Fountzila A, Zaramboukas T, Sombolos K, Destouni-Salem E, Vritsios A, Tourkantonis A. Induction chemotherapy with a new regimen alternating cisplatin, fluorouracil with mitomycin, hydroxyurea, and bleomycin in carcinomas of nasopharynx or other sites of the head and and neck region. Cancer 66:1453–1460, 1990.
21. Fountzilas G, Kosmidis P, Makrantonakis P, Sridhar SK, Banis K, Themelis C, Kalogera-Fountzila A, Avramidis V, Beer M, Sombolos K, Vritsios A, Daniilidis A. Carboplatin, continuous infusion fluorouracil and mid-cycle high-dose methotrexate as initial treatment in patients with locally advanced head and neck cancer. Tumori 77:426–431, 1991.
22. Fountzilas G, Kosmidis P, Sridhar S Kasi, Kalogera-Fountzila A, Bannis K, Dimitriadis A, Avramidis V, Nicolaou A, Zaramboukas T, Skarlos D, Vritsios A, Daniilidis J. Cisplatin and continuous infusion of fluorouracil followed by radiation and weekly carboplatin in the treatment of locally advanced head and neck cancer: A Hellenic Cooperative Oncology Group study. Cancer Inv 14: 189–196, 1996.
23. American Joint Committee on Cancer: Manual for Staging on Cancer, 3rd ed. Philadelphia, JB Lippincott, 27–51, 1988.
24. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. Cancer 47:207–214, 1981.
25. Woolson, RF (ed): Statistical Methods for the Analysis of Biomedical Data. New York: John Wiley and Sons, 1987.
26. Hosmer DW, Lemeshow S (eds): Applied Logistic Regression. New York: John Wiley and Sons, 1989.
27. Kaplan EL, Meier P: Non parametric estimation from incomplete observations. J Am Stat Assoc 53:457–481, 1958.
28. Mantel M: Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep 50: 163–170, 1966.
29. Cox DR: Regression models and life tables. J Roy Statist Soc 34 (Series B):187–220, 1972.
30. Andersen PK: Testing goodness of fit of Cox's regression and life model. Biometrics 38:67–77, 1982.
31. Dixon WJ, Brown MB, Engleman L: (eds) BMDP Statistical Software Manual. Los Angeles: University of California Press, 1990.
32. Papavasiliou C. Cancer of the nasopharynx. Incidence, clinical course and results of therapy: a report from Greece. Clin Radiol 25:409–414, 1974.
33. Hubert A, De The G. Comportement alimentaire, modes de vie et cancer du rhinopharynx. Bull Cancer (Paris). 69:476–482, 1982.
34. Cognetti F, Pinnaro P, Ruggeri EM, Carlini P, Perrino A, Impiombato FA, Calabresi F, Chilelli MG, Giannarelli D. Prognostic factors for chemotherapy response and survival using combination chemotherapy as initial treatment of advanced head and neck squamous cell cancer. J Clin Oncol 7:829–837, 1989.
35. Pennacchio JL, Hong WK, Shapshay S, Gillis T, Vaughan C, Bhutani R, Ucmakli A, Katz AE, Bromer R, Willet B. Combination of cisplatin and bleomycin prior to surgery and or radiotherapy compared with radiotherapy alone for the treatment of advanced squamous-cell carcinoma of the head and neck. Cancer 50:2795–2801, 1982.
36. Hill BT, Price LA, MacRae K. Importance of primary site in assessing chemotherapy response and 7-year survival data in advanced squamous-cell carcinomas of the head and neck treated with initial combination chemotherapy without cisplatin. J Clin Oncol 4:1340–1347, 1986.
37. Bachaud JM, David JM, Shubinski RE, Perineau D, Boussin G, Serrano E, De Forni M, Pessey JJ, Daly-Schveitzer NJ. Predictive factors of a complete response to and adverse effects of a CDDP-5FU combination as primary therapy for head and neck squamous carcinomas. J Laryngol Otol 107:924–930, 1993.
38. Jacobs C, Makuch R. Efficacy of adjuvant chemotherapy for patients with resectable head and neck cancer: a subset analysis of the head and neck contracts program. J Clin Oncol 8:838–847, 1990.
39. Ervin TJ, Clark JR, Weichselbaum RR, Fallon BG, Miller D, Fabian RL, Posner MR, Norris CM, Tuttle SA, Schoenfeld DA, Price KN, Frei E III. An analysis of induction and adjuvant chemotherapy in the multidisciplinary treatment of squamous-cell carcinoma of the head and neck. J Clin Oncol 5:10–20, 1987.

40. Shapshay SM, Hong WK, Incze JS, Sismanis A, Bhutani R, Vaughn CW, Strong MS. Prognostic indicators in induction cisplatinum bleomycin chemotherapy for advanced head and neck cancer. Am J Surg 140:543–548, 1980.
41. Davis RK, Stoker K, Harker G, Davis K, Gibbs FA, Harnsberger HR, Stevens MH, Parkin JL, Johnson LP. Prognostic indicators in head and neck cancer patients receiving combined therapy. Arch Otolaryngol Head Neck Surg 115:1443–1446, 1989.
42. Vokes AA, Athanasiadis I. Chemotherapy for squamous-cell carcinoma of the head and neck: the future is now. Ann Oncol 7:15–29, 1996.
43. Kaye SB. Ovarian cancer, from the laboratory to the clinic: Challenges for the future. Ann Oncol 7:9–13, 1996.
44. Scambia G, Ferrandina G, Marone M, Panici PB, Giannitelli C, Piantelli M, Leone A, Mancuso S. nm23 in ovarian cancer: Correlation with clinical outcome and other clinicopathologic and biochemical prognostic parameters. J Clin Oncol 14:334–342, 1996.
45. Crissman JD, Pajak TF, Zarbo RJ, Marcial VA, Al-Sarraf M. Improved response and survival to combined cisplatin and radiation in non-keratinizing squamous-cell carcinomas of the head and neck. Cancer 59:1391–1397, 1987.